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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,978	01/09/2001	Eugene Roussel	210582.0001/1US	6809

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DUANE MORRIS, LLP
ATTN: WILLIAM H. MURRAY
ONE LIBERTY PLACE
1650 MARKET STREET
PHILADELPHIA, PA 19103-7396

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	22

DATE MAILED: 04/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/756,978	ROUSSEL, EUGENE	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-14-2003 has been entered.

Claims 1-66 are pending and examined on merits.

Claim Rejections - 35 USC § 112

Claims 2, and 4-6 **remain rejected** under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to method of inducing cancer cell death using proteases plus three other agents for inducing cancer cells. This rejection is based on use of protease in inducing cancer cell death. Applicant does not argue that proteases have been used as cancer therapy in the art. Although one medical theory indicates that extracellular-matrix breakdown might be a signal for body's immune system to get ready for some serious work (see Gallucci et al, 2001, Curr Opin Immunol, vol. 13, pages 114-9), the current state of art indicates proteases production is increased in tumor cells in order to metastasizes, therefore inhibition of proteases, especially metalloproteases in body, not administering them leads to cancer cell death. See Dabrowska et al (2000, Anticancer Res, vol. 20, pages 391-4 abstract only), Kondoh et al (2003, Breast Cancer Res Treat, vol. 78, pages 37-44), or Yamamoto et al (2003, Int J Cancer, vol. 103, page 822 abstract only). Considering the state of art, including the discussion in Dr. Roussel's declaration, it is maintained that one skilled in the art would have reasons to question the efficacy of the claimed treatment method. In the absense of a working example or other evidence of

the method's effectiveness, it is maintained that undue experimentation would be required to practice the invention as claimed.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "tumor de-bulking agent" but it is not clear what the metes and bounds are for the limitation. The specification at page 10 line 10 appears to suggest the "tumor de-bulking agent" means proteases. Is there any differences between "tumor de-bulking agent" and proteases in terms of what is being claimed for patent protection?

Claims 11 and 12 recite "concentrated" but it is not clear what the metes and bounds are.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83).

The claims are drawn to method of human cancer treatment by local administration (i.e., directly injecting into tumor cells) of four active ingredients, i.e., 1) antigen-releasing agent 2) leukocyte attractant 3) interferon gamma 4) a second type 1

inflammatory response promoting agent. "Antigen-releasing agent" is not art-defined term but the molecules listed in instant claims 2-12 indicates that the limitation "antigen-releasing agent" appears to encompass any apoptosis-inducing agent (see the instant claim 3). Lee et al teach at Fig. 1C at page 233 that anti-Fas antibody (one of "antigen-releasing agent") in combination with IFN-gamma, and TNF (a second type 1 inflammatory response promoting agent) has the hightest anti-tumor effect. Injecting directly to tumor is obvious variation of Lee et al administration since the specification does not show any unexpected result and injecting directly to tumor is a known method (see below). Tannenbaum et al are cited to show that several cytokines applicant calls "leukocyte attractant" are known in the art to have anti-tumor effects. Lanni et al are cited to show that it is well known in the art that combination therapy have been used to minimize and/or avoid chemotherapeutic resistance by tumor cells. Note abstract and Fig. 3. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine known anti-tumor agents to kill tumor cells in a human patient because inducing tumor cell death in a human patient is desirable. Since the specification does not teach any unexpected result, different administration schedule is an obvious variation of known schedule.

Claims 7-9 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Zeisig et at al (provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19; Anticancer Research, 1994, vol. 14, page 1785-1790).

The claims are drawn to the method of the base claim (see above) using the products in instant claims. Zeisig et al teach all of the products in the instant claims have tumor cytotoxic effects. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use known tumor cytoxic agents to induce tumor cell death in a human patient.

Claim 10 is rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Chou et al (1997, Bioelectromagnetics, vol. 18, page 14-24, abstract only) or Habal (1980, J Biomer Mater Res, vol. 14, pages 789-801, abstract only), Jaroszeski et al (1997, Biochim Biophys Acta, vol. 1334, pages 15-18), or Wemyss-Holden et al (2000, J Surg Res, vol. 93, pages 55-62).

The claims are drawn to the method of the base claim (see above) using electric current as antigen releasing agent. Any one of the four references teaches electric current has anti-tumor effect. Combining known anti-tumor therapy for inducing tumor cell death is obvious.

Claim 11 and 12 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 3 above, and further in view of Tamai et al (2000, Oncol Rep, vol. 719, pages 719-23).

The claims are drawn to the method of the base claim (see above) using either acid or base as antigen releasing agent. Tamai et al teach either strong base or acid has anti-tumor effect. The reference also gives guidance about what concentration of acid is appropriate and therefore the acid in instant claim 11 is obvious variation of the acid in the prior art since the instant specification does not teach any unexpected result with the recited specific acids. Combining known anti-tumor therapy for inducing tumor cell death is obvious.

Claims 17 and 18 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claim 1 above, and further in view of Wuyts et al (provided with

Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19, 1994, Journal of Immunological Methods, vol. 174, pages 237-247).

The claims further specify leukocyte attractant of the base claim. Wuyts et al teach proteins specified in the instant claims.

Claims 30, and 40-66 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Lee et al (J Immunol. 2000 Jan 1: 164: 231-9) in view of Tannenbaum et al (J Immunol. 1998: 161: 927-932) or Lanni et al (Proc Natl Acad Sci USA vol. 94, pages 9679-83) as applied to claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 above, and further in view of Greenberg (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), Parslow (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), Akatov et al (2000, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19), and Oppenheim et al (1997, provided with Dr. Roussel's Declaration filed on 1-14-2003, Paper No. 19).

The references teach all of the products in the instant claims have either anti-tumor effects or good in patients going through anti-tumor therapy. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use products good for anti-tumor therapy to induce cancer cell death. The specification does not teach any unexpected results, combining known compounds good for anti-tumor effects for inducing cancer cell death is obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
April 6, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600